REMARKS

The Applicants thank the Examiner for her discussion in the Advisory Action for maintaining her rejections of claims 21-22 under U.S.C. 103(a).

The Applicants request the entry of amendments to Claim 21 to more clearly differentiate the claimed invention from the prior art. The Applicants are amending Claim 21 to indicate that the method for preventing footrot and liver abscesses require that the vaccine administered to the animal contains **unconcentrated** Fusobacterium necrophorum cell culture and that the bacteria cells remain whole (they are NOT broken open through sonication). Without breaking open the bacteria cells, the intracellular components of the bacteria are NOT exposed as antigens, even after inactivation with formaldehyde. The only components exposed as antigens are the extracellular components – those secreted into the cell culture and those that are located on the outside of the bacteria, on the outer membrane or cell wall.

The Applicants point out that Garcia et al. discloses sonicating the bacteria cell culture to break open the bacteria cells (page 223, column 2, lines 2-4). By having whole bacteria cells, not bacteria cells broken open, the Applicants believe that Garcia et al. fails to teach the invention.

The Applicants note that Clark et al. concentrates the *F. necrophorum* culture prior to the formation of the vaccine (page 107, 2nd column). In contrast, the Applicants lack a concentration step and use only non-concentrated cell culture in the vaccine. As such, the Applicants believe that Clark et al. fails to teach the invention.

35 U.S.C. § 103(a)

The Examiner maintained the rejections of Claims 21 and 22 under U.S.C. 103(a) with two arguments. For the first argument the Examiner cited Garcia et al. in view of Emery et al. In the second argument, the Examiner cited Garcia et al. in view of Clark et al.

Turning to the first argument by the Examiner, citing Garcia et al. in view of Emery et al., the Applicants would like to point out that in Section A of the Examiner's Response to Applicants' Arguments comments, the Examiner states that Garcia et al. teaches that the vaccine compositions were "... prepared from **sonicated**, unfractionated cells (whole cells)." (emphasis added).

The Applicants kindly point out that sonication breaks cells open. A thorough sonication of cells results in no whole cells remaining. On page 223, column 2, lines 2-4, Garcia et al. wrote that "[c]ells were ruptured ultrasonically for 18-20 min in a MSE 100 sonic vibrator." This length of sonication is enough to rupture all or almost all bacterial cells in the fluid. According to Garcia et al., "An almost complete disruption of the cells by this technique was observed by phase microscopy." (See page 223, 2nd column, lines 4-6) In the footnotes to Table 1 on page 225, the "sonicated toxoid" is "[w]hole organism disrupted ultrasonically and formalized, alum precipitated". The "cytoplasmic toxoid" is "crude bacterial cell extract minus the cell walls, alum precipitated.

Thus, it appears that Garcia et al. did NOT use whole cells in their vaccine. Rather Garcia et al. broke open the cells and used, in one preparation, the broken open cells (containing both the intracellular and cell wall components), and, in the other preparation, just the cytosolic components. As such, Garcia et al. allowed the cytosolic components to be exposed as antigens in both preparations, in contrast to the claimed methods.

Furthermore, Garcia et al. teaches that the vaccine containing just the intracellular components are more effective than the vaccine containing the intracellular components and the cell walls. According to the data in Table 1 on page 225, the "sonicated toxoid" had more abscesses per liver than the two different "cytoplasmic toxoid" preparations. Thus, even if there were a few whole cells left in the sonicated toxoid, Garcia et al. teaches away from using a vaccine preparation with whole cells. Garcia et al. teaches that it would be better to use the cytosolic components in a vaccine rather than just the outer membrane components in a vaccine.

Emery et al. does not remedy this aspect of Garcia et al. because Emery et al. does not discuss vaccines for *F. necrophorum*.

Thus, Applicants believe that Garcia et al. in view of Emery et al. fails to establish that the methods claimed are taught or obvious to one skilled in the art because the Applicants' method requires whole, unruptured cells of *F. necrophorum*. Because the cells are NOT broken open, the cytosolic or intracellular components are not be exposed as antigens. This aspect is in direct contrast to Garcia et al. which teaches that the intracellular components provide a better protection as a vaccine than the cell wall components.

Because Garcia et al. in combination with Emery et al. does not teach nor make obvious the Applicants' invention, the Applicants kindly request the withdrawal of this rejection.

Turning to the second argument, of Garcia et al. in light of Clark et al., the Applicants reiterate that Garcia et al. uses sonicated cells, not whole cells in their vaccine.

While Clark et al. uses a whole cell vaccine (page 107, 2nd column), it contains **concentrated** *F. necrophorum* culture, "... concentrated 10 times using a XM100 A membrane with MW retention of 100,000." (page 107, 2nd column). Clark et al. also used a concentrated cytoplasmic fraction. This concentrated whole cell vaccine provided 25% protection, compared to the 37.5% protection of a concentrated cell-free cytoplasmic fraction vaccine, in infected cattle (see page 109, 2nd column, first 10 lines of Discussion section, and page 107, 2nd column describing the vaccine given to each group). Based on these results, Clark et al. appears to teach away from using whole cell vaccine made with a concentrated cell culture. Furthermore, Clark et al. does NOT teach using an non-concentrated whole cell vaccine which the Applicants are claiming.

In light of the teachings of Garcia et al. and Clark et al., the methods claimed by the Applicants provide surprising results, in that the methods protect bovine from infections of *F. necrophorum*. After all, Garcia et al. appears to teach that one has better protection using the intracellular fraction of inactivated bacteria than a vaccine containing broken open bacteria cells (not even whole cells). And Clark et al. teaches that concentrating the intracellular fraction produces better results than a concentrated whole cell vaccine. If one of ordinary skill in the art would, upon reading Clark et al. and Garcia et al., conclude that an non-concentrated whole cell vaccine without exposure to intracellular components would not provide protections against diseases causes by *F. necrophorum*.

Garcia et al. fails to teach or alternatively teaches away from using an non-concentrated, whole cell vaccine. Clark et al. fails to remedy this deficiency because Clark et al. fails to teach using an non-concentrated, whole cell vaccine. Thus, the rejection based on Garcia et al. in light of Clark et al. is inappropriate. But, even if Garcia et al. and Clark et al. could be considered to teach a method of preventing footrot and liver abscesses caused by *F. necrophorum* by administering to the bovine a vaccine containing non-concentrated, whole cell *F. necrophorum* grown for 10 to 18 hours with a bacterial count population equal to at least 1 x 10^5 CFU/ml and using formaldehyde to inactivate the whole cell culture, the results presented by Applicants provide surprising results based on the teachings of Garcia et al. and Clark et al. As such, the Applicants request withdrawal of this rejection.

Potential 35 U.S.C. § 102(b) Rejection

The undersigned thanks the Examiner for reviewing the information the undersigned submitted in the After Final Response.

As a result of an on-going investigation, the undersigned was presented with a document that appears to be a letter sent to Dr. Robert J. Danielson, Marketing Director of MWI Veterinary Supply Company. A copy of this letter is enclosing and labeled as Attachment A. The letter contains the date September 3, 1998, written by hand on the upper right corner. The undersigned does not know whose handwriting it is. The attached letter states that efficacy data, product description and a copy of the label was enclosed with the letter, but the undersigned lacks copies of these documents. However, the undersigned notes that the bacterin referred to in this letter as "Fusogard" is the bacterin described in the pending patent application. The efficacy date most likely contains the data presented in the patent application which demonstrate that the claimed vaccine and method are effective. The dosage mentioned in the letter is within the range of dosage claimed in Claim 21. The letter also states that the vaccine was approved for use in cattle for the prevention of footrot (presumably by the USDA, see below), one aspect of the method claimed in Claim 21.

The undersigned notes that September 3, 1998 is more than one year prior to the earliest filing date of this patent application.

The undersigned also would like to provide the Examiner with a copy of the Center for Veterinary Biologic Notice No. 98-09 dated July 8, 1998 indicated that the USDA issued a license for a *Fusobacterium necrophorum* bacterin to ImmTech Biologics, Inc., the original assignee of this patent application. A copy of this document is attached as Attachment B. According to this document, the CVB of the USDA issued the licensure for sale of the vaccine on June 8, 1998. This vaccine is the one described in the pending patent application and covered by the claims for the use in cattle to prevent footrot. This USDA approval date and date of the official publication are more than one year prior to the earliest filing date of this patent application. They also is several months prior to the date written on the letter, Attachment A.

The undersigned is bringing this information to the Examiner's attention in order to comply with the undersigned's duty of disclosure under 37 C.F.R. § 1.56.

Should the Examiner have any questions or believes that an interview would be useful for the prosecution of this application, the Examiner is requested to contact the undersigned at the telephone number indicated.

The Commissioner is authorized to deduct any fees required to maintain the pendency of this patent application from Applicants deposit account, 19-0134.

Respectfully submitted,

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Date: March 20, 2006